IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

ATTY.'S DOCKET: SCHIAFFONATI=1

In re Application of:	)	Art Unit: 1646
SCHIAFFONATI et al.	)	Examiner: P. M. Mertz
Appln. No.: 10/583,370	)	Washington, D.C.
Date Filed: June 18, 2007	)	Confirmation No. 8192
For: USE OF IL-6 IN LIVER INJURY	)	

DECLARATION UNDER 37 CFR §1.132

Honorable Commissioner for Patents
U.S. Patent and Trademark Office
Customer Service Window
Randolph Building, Mail Stop
401 Dulany Street
Alexandria, VA 22314

Sir:

I, Michel Dreano, hereby declare and state as follows:

I am a co-inventor of the above-identified application and my educational and professional experience is presented in the curriculum vitae attached hereto.

I understand that the claims to a method for treating liver cirrhosis have been rejected under 35 U.S.C. §103(a) as being unpatentable over Kovalovich et al., *J. Biol. Chem.* 276(28):26605-26613 (2001), because the examiner takes the position that it would be obvious to therapeutically administer low dose IL-6 to treat liver cirrhosis according to

the present invention in view of Kovalovich's disclosure of pre-treatment with a much higher dose of IL-6 prior to induced liver injury. I also understand that the claims have been rejected under 35 U.S.C. §112, first paragraph, as lacking enablement for the scope claimed, where the examiner is taking the position that the instant specification is only enabling for treatment of chemical cirrhosis and not for other causes of liver cirrhosis.

I will first address the obviousness rejection over Kovalovich as to why it is not obvious to try therapeutic treatment for liver cirrhosis when pre-treatment is known. The following examples from among numerous examples in the literature are presented to support the position that compounds exhibiting beneficial effects when administered before the onset of a pathological situation (pre-treatment) would NOT be expected to be effective when administered therapeutically to treat the pathological situation.

The first example is from the, Gardiner et al., *Br. J. Pharmacol*. 128:1778-1782 (1999), reference attached hereto, which reported that, using a rat model of vasodilation induced by infusion of liposaccharides, pre- or post-treatments with glibenclamide (potassium-ATP channel antagonist) result in different biological effects. Indeed, whereas pre-treatment abolished the initial hypotension but not renal vasodilation,

post-treatment instead led to a significant increase in mean arterial blood pressure and reduction in renal conductance.

Similarly, in the second example from Hom et al., *J. Pharmacol. Exp. Therap.* 272:452-459 (1995), a copy of which is attached hereto, significant differences between pre- and post-treatments were observed using a LPS-induced hypotension and vascular hypo-reactivity rat model. Pre-treatment with dexamethasone significantly attenuated LPS-induced norepinephrine hypo-responsiveness, while post-treatment had no effect. Interestingly, in parallel experiments, the authors showed that N-monomethyl-L-arginine (LNMMA) induced hypo-responsiveness after both pre- or post-treatments.

Many other examples showing such differences between pre- and post-treatments can be found in the scientific literature. For example, many compounds are effective to prevent the onset of clinical symptoms in animal models of stroke. However, none of these compounds display robust protective effect when administered therapeutically (post-treatment). It would be well recognized and expected by those of ordinary skill in the art that, in many pathological conditions, irreversible events, e.g., cell death, occur and therefore any post-treatment would be ineffective.

Interestingly and more surprisingly, there are also examples of compounds that can be active after a therapeutic

treatment but NOT after a preventative treatment. The results reported in Di Marvo et al., *J. Neuroimmunol*. 116:168-177 (2001), a copy of which is attached hereto, clearly show that daily s.c. administration of IL-6 in rats starting at the peak of experimental allergic encephalomyelitis significantly reduced the clinical disease course (i.e., reduced the number and diminished the severity of relapses), while an early IL-6 treatment before the onset of clinical signs did not alter the progression of the disease.

Those of ordinary skill in the art taking into account the above examples and observations would conclude that a pre-treatment effect cannot predict the post-treatment effect and vice versa. Accordingly, Kovalovich cannot lead one of ordinary skill in the art to the presently claimed method for treating liver cirrhosis.

With regard to the lack of enablement rejection, the CCl_4 model exemplified in the instant specification is well accepted in the art as a general liver cirrhosis model, not just for chemically induced cirrhosis. The Jang et al., *Transplant Proceedings* 40:2700-2703 (2008) paper, a copy of which is attached hereto, on the evaluation of the model of hepatic fibrosis teaches at page 2700, first column, that "Hepatic cirrhosis by toxic drugs such as…, carbon tetrachloride (CCl_4), … are the most popular experimental

model." Furthermore, in the "Discussion" section, it is taught that CCl_4 administration showed the greatest incidence and the highest reproducibility of fibrosis.

It is also taught in the abstract of Weber et al., *Crit. Rev. Toxicol.* 33(2):105-136 (2003), a copy of which is attached hereto, that "Yet CCl_4 continues to provide an important service today as a model substance to elucidate the mechanisms of action of hepatotoxic effects such as fatty degeneration, fibrosis, hepatocellular death, and carcinogenicity."

In conclusion, Kovalovich cannot make obvious the presently claimed method, and the instant specification, including the CCl_4 model exemplified therein, is indeed well enabled for liver cirrhosis in general, not just for chemically induced cirrhosis.

The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such

willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date June 02, 2009	/Michel DREANO/

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EDUCATION

PhD in Microbiology (1983)
Specialisation in Molecular Virology (University of Paris 7/Pasteur Institute, Paris, France)

PhD in Cell Biology (1989)
Specialisation in Cell and Molecular Biology (University of Burgundy, France)

LANGUAGES

French
Mother tongue

English
Fluent (business & scientific)

PERSONNAL DATA

French, 52, married
Two daughters, 21 and 18
Driving licence

Hobbies
Trekking, Scuba Diving, Handball trainer (BEES1), Mountain bike, ski

EXPERIENCE

Serono International SA (SISA) since 1989 :
1989: Drug Development Associate - SISA
1991: Manager for Cellular Biology - SISA
1995: Manager – Discovery -SISA
1996: Associate Director - Academic Collaboration - SISA
1997: Associate Director Cell Biology - SISA
2003: Associate Director - Research Alliance Management (RAM)
2004: Director – RAM at SISA
Director – RAM at Serono Research Institute - USA
2006: Director – RAM at SISA at Geneva
2007: Director Research Strategic Innovation and Research Portfolio Management at Merck Serono International SA

Research Alliance Management

- Coordination of research and development programs and contracted projects involving industrial/academic partners from basic research to clinic
- Management of international project teams (EU/USA/IL). Management of cross-functional transversal teams (Drug Discovery, Development, Toxicology)
- Coordination of a 9-years research project from gene discovery to clinical developments of small molecule Ikappa B kinase inhibitors with current applications in leukemic patients
- Project leader pharmacological developments of IL-6 from basic research up to experimental pharmacology in Chemotherapy/ Diabetes Induced Poly Neuropathy
- Management and rationalisation of a project research from protein expression to preclinical developments with possible applications in metabolic diseases/thrombosis
- Design, setting up and follow up of commercial contacts with the numerous academic institutions, Contract Research Organization
- Search and scientific evaluation of Research Projects proposed by Academic Institutions
- Interface with Legal and Intellectual Property groups
- Writing of abstracts, publications and communications.
- Presentations of company activities to external collaborators

1988-1989 Intracel S.A. (start up), Genetic Engineering Group, Geneva, Switzerland
Section Manager: Expression of recombinant proteins by eukaryotic cells using promoters of heat shock protein.

1984-1988 Battelle Memorial Institute, Genetic Engineering Group, Geneva, Switzerland
Project leader: Expression of recombinant proteins by eukaryotic cells using promoters of heat shock protein
- Managing scientific developments of a 5 years projects
- Leading of a scientific team
- Contract Research
- Participation in the realisation of a Multiclient Study
- Elaboration of Patent Applications and writing scientific publications
- Collaborative Marketing with Private Companies and Government agencies
- Initialisations of scientific collaborations with private or public laboratories
- Participation in a Venture leading to the creation of IntraCel S.A.

1980 -1984: Unit of Molecular Virology – Pasteur Institute, Paris:
Researcher: Molecular Cloning of the poliovirus genome and expression of cloned sequences in eukaryotic cells.

SCIENTIFIC INTERESTS

Oncology
Main interests: Acute/chronic myeloid leukaemia, multiple myeloma, cutaneous T cell lymphoma, solid tumors
- **In vivo models**
- Xenotransplant models of various human cancer cell lines, primary samples from AML or MM patients.
- Syngenic cancer models
- **External collaborations:**
  JF Peyron (Nice, France), B. Klein (Montpellier, France), C. Chomienne (Paris, France), H. Bachelez (Paris, France), C. Dumontet (Lyon, France), J. Shaughnessy (Little Rock, US), van Etten (Boston, MA), G. Forni (Turin, Italy), M. Gianni (Milan, Italy), Oncotest (Frieburg, Germany)

Neurology
Main interests: Multiple sclerosis and induced neuropathies (diabetic neuropathy, toxic neuropathies),
In vivo models:
- Models of multiple sclerosis in rats and mice: EAE chronic and acute models…
- Models of induced neuropathies: cisplatin, vincristine and taxol, diabetic neuropathies, trauma nerve injuries (optic and peripheral nerves)
- **External Collaborations:**
  Neurofit SA (Strasbourg, France); Cerep (Paris, France), MDS (Plan-Les-Ouates, Switzerland), T. Olsson (Stockholm, Sweden), H. Wekerle (Martinsried, Germany), N. Cameron (Aberdeen, UK), J. Glass (Emory, USA), M. Revel (Rehovot, Israel), M. Pizzi (Brescia, Italy), F. Nicoletti (Catania, Italy), N. Déglon (Lausanne, Switzerland)

Rheumatoid arthritis
- **In vivo models:** Models of rheumatoid arthritis in rats and mice: collagen induced arthritis, antigen induced arthritis
- **External Collaborations:** J. Leceta (Madrid, Spain), G. Firestein (San Diego, USA)

Metabolic diseases

- **In vivo models:** Models of types 1 and 2 diabetes, obesity, non-alcoholic steatohepatitis
- **External collaboration:** H. Lodish (Boston, USA), B. Bihain (Nancy, France), Physiogenex (Toulouse, France), Ciphergen (Basel, Switzerland), C. Trautwein (Aachen, Germany)

Other therapeutic areas

Liver diseases, Cachexia, Immunology, Virology, Inflammatory Bowel Diseases

Preclinical developments

Toxicology, safety

COMMUNICATIONS / PUBLICATIONS

Lounnas N., Frelin C., Gonthier N., Colosetti P., Sirvent A., Cassuto J.-P., Berthier F., Sirvent N., Rousselot P., **Dreano M.**, Peyron J.-F., Imbert V. 2009. NF- kB inhibition triggers death of imatinib-sensitive and imatinib-resistant chronic myeloid leukemia cells including T315I Bcr-Abl mutants. Int. J. Cancer: 125, 308-317.

Griessinger E., Hélias V., Cuburu N., Imbert V., Frelin C., Dageville C., Hummelsberger M., Sirvent N., **Dreano M.**, Peyron J.F. 2008. Pre-clinical targeting of NF-kB and Flt3 pathways in AML cells. Leukemia 22, 1466-1469.

Callizot N., Andriambeloson E., Glass J., Revel M., Ferro P., Cirillo R., Vitte P.-A., **Dreano M**. 2008. Interleukin-6 protects against paclitaxel, cisplatin and vincristine-induced neuropathies without impairing chemotherapeutic activity. Cancer Chemother Pharmacol. 62, 995-1007.

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Beraza N., Malato Y., Vander Borght S, Liedtke C., Wasmuth H.E., **Dreano M.**,.de Vos R., Roskams T., Trautwein C. 2008. Pharmacological IKK2 inhibition blocks liver steatosis and initiation of non-alcoholic-steatohepatitis. Gut 57, 655-663

Lagadec P., Grissinger E.; Nawrot M.-P.; Fenouille N., Colosetti P., Imbert V.; Mari M.; Hofman P.; Czerucka D.; Rousseau P.; Berard E; **Dreano M.**; Peyron J.-F. 2008. Pharmacological targeting of NF-kB potentiates the effect of the topoisomerase inhibitor CPT-11 on colon cancer cells. Br J Cancer 98, 335-344.

Sors A., Jean-Louis F, Bégué E., Parmentier L., Dubertret L., **Dreano M**., Courtois G., H. Bachelez, L. Michel. 2008. Inhibition of IKK2 in cutaneous T cell lymphoma dowregulates NF-kappaB constitutive activation, induces cell death and potentiates the apoptotic response to antineoplastic chemotherapeutic drugs. Clin. Cancer Res. 14, 901-911.

Romagnoli M., Desplanques G., Maiga S., Legouill S., **Dreano M.**, Bataille R., Barillé-Nion S. 2007. Inhibition of the canonical NF-kB pathway blocks myeloma cell growth and induces apoptosis in strong synergy with TRAIL. Clinical Cancer Research 13, 1-9.

Tiberio GAM, Tiberio L., Benetti A., Cervi E., Pandolfo G., **Dreano M**., Garotta G., Comini L:, Martini M., Giulini SM, Schiaffonatti L. 2007. Interleukin-6 sustains hepatic regeneration in cirrhotic rat. Hepato-Gastroenterology 54, 878-883.

Jourdan M., Moreaux J., De Vos J., Hose D., Mahtouk K., Abouladze M., Robert N., Baudard M., Reme T., Romanelli A., Rossi J.-F., Goldschmidt H., **Dreano M.**, Klein B. 2007 Targeting NFkB pathway with an IKK2 inhibitor induces inhibition of multiple myeloma cell growth. Br. J. Haematol. 138, 160-168.

Griessinger E., Imbert V., Dubreuil P., **Dreano M.**, Peyron J.-F. 2007. Dual inhibition of NFKB and FLT3 by a small molecule inhibitor of IKK2 to target AML cells. Leukemia 21, 877–885.

Tiberio L., Tiberio GAM., Bardella L., Cervi E., Cerea K., **Dreano M.**, Garotta G., Fra A., Montani N., Ferrari-Bravo A., Callea F., Grigolato P., Giulini SM., Schiaffonatti L. 2006. Mechanism of interleukin-6 protection against ischemia-reperfusion injury in rat liver. Cytokine 34, 131-142.

Andriambeloson E., Baillet-Mignard C., Vitte PA., Garotta G., **Dreano M.**, Callizot N. 2006. Interleukin-6 prevents the development of experimental diabetes-related neuropathy. Neuropathology 26, 32-42.

Comini L., Pasini E., Bachetti T., **Dreano M.**, Garotta G., Ferrari R. 2005. Acute Haemodynamic Effects of IL-6 Treatment In Vivo: Involvement of Vagus Nerve in NO-Mediated Negative Inotropism. Cytokine 30, 236-242.

Frelin C., Imbert V., Griessinger E., Peyron AC., Rochet N., Philip P., Dageville C., Sirvent A., **Dreano M.**, Sirvent N., Peyron JF. 2005. Targeting NF-kB activation via pharmacological inhibition of IKK2 induced apoptosis of human Acute Myeloid Leukemia cells. Blood 105, 804-811.

Heckmann A, Waltzinger C., Jolicoeur P., **Dreano M.**, Kosco-Vilbois M. and Sagot Y. 2004. NK-kB inhibitor alleviates kidney and wasting diseases in a model of human AIDS. Am. J. Pathol.164, 1253-1262.

Caposio P., **Dreano M.**, Garotta G., Gribaudo G., Landolfo S. 2004. Human cytomegalovirus activates cellular IKK2 activity and requires the enzyme for productive replication. J. Virol. 78, 3190-3195

Pizzi M., Sarnico I., Boroni F., Benarese M., **Dreano M.**, Garotta G., Valerio A., Spano PF. 2004. Interleukin-6 (IL-6) and IL6 receptor/IL6 fusion protein prevent neuron and oligodendrocyte degeneration in organotypic hippocampal slices exposed to excitotoxic injury. Mol. Cell. Neurosci. 24, 301-311.

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Valerio A., Ferrario M., **Dreano M.**, Garotta G., Spano P., Pizzi M. 2002. Soluble interleukin-6 (IL-6) receptor/IL-6 fusion protein enhances in vitro differentiation of purified rat oligodendroglial lineage cells. Mol. Cell. Neurosi. 21, 602-15.

Bensadoun JC., de Almeida LP., **Dreano M.**, Aebischer P., Deglon N. 2001. Neuroprotective effect of interleukin-6 and IL6/IL6R chimera in the quinolinic acid rat model of Huntington's syndrome. Eur. J. Neurosci. 14, 1753-1761.

Prigent P., El Mir S., **Dreano M.**, Triebel F. 1999. Lymphocyte activation gene-3 induces tumor regression and antitumor immune responses. Eur. J. Immunol. 29, 3867-3876.

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Jiang X., **Dreano M.**, Buckler DR., Cheng S., Ythier A., Wu H., Hendrickson WA., El Tayar N. 1995 Structural predictions for the ligand-binding region of glycoprotein hormone receptors and the nature of hormone-receptor interactions. Structure. 3, 1341-1353.

L'Hote P., Alouani S., Marq JB., Montandon F., Chessebeuf-Padieu M., **Dreano M.** 1993. Concomitant cellular expression of heat shock regulated genes of hepatitis B virus surface antigen and of human growth hormone by a NIH-3T3 cell line. Cell Biol. Toxicol. 9, 319-332.

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Bearzotti M., Perrot E., Michard-Vanhee C., Jolivet G., Attal J., Theron MC., Puissant C., **Dreano M.**, Kopchick JJ., Powell R., Gannon F., Houdebine LM., Chourrout D. 1992. Gene expression following transfection of fish cells. J. Biotechnol.. 26, 315-325.

Alouani S., L'Hote P., Marq JB., Houdebine LM., Montandon F., Chessebeuf-Padieu M., **Dreano M.** 1992. Expression of heat shock-regulated human growth hormone genes containing or lacking introns by NIH-3T3 and Wish cell lines. Cell Biol. Toxicol. 8, 139-156.

Fischbach M., Cao HW., Diez Ibanez M., Tsaconas C., Alouani S., Montandon F., El Baraka M., Padieu P., **Dreano M.**, Chessebeuf-Padieu M. 1991. Maintenance of liver function in long term culture of hepatocytes following in vitro or in vivo Ha-rasEJ transfection. Cell Biol. Toxicol. 7, 327-345.

Dreano M., Marq JB. and Bromley P. 1988. Antibody formation against heat-induced gene products expressed in animals. Bio/Technol. 6, 1340-1343

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Dreano M., Fouillet X., Brochot J., Vallet JM., Michel ML., Rungger D., Bromley P. 1987. Heat-regulated expression of the hepatitis B virus surface antigen in the human Wish cell line. Virus Res. 8, 43-59.

Amin J., Mestril R., Schiller P., **Dreano** M., Voellmy R. 1987. Organization of the Drosophila melanogaster hsp70 heat shock regulation unit. Mol. Cell. Biol. 7, 1055-1062.

Dreano M., Brochot J., Myers A., Cheng-Meyer C., Rungger D., Voellmy R., Bromley P. 1986. High-level, heat-regulated synthesis of proteins in eukaryotic cells. Gene. 49, 1-8.

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van der Werf S., **Dreano M.**, Bruneau P., Kopecka H., Girard M. 1983. Expression of poliovirus capsid polypeptide VP1 in Escherichia coli. Gene. 23, 85-93.

Kopecka H., van der Werf S., Bregegere F., Kitamura N., **Dreano M.**, Rothberg PG., Wimmer E., Kourilsky P., Girard M. 1981. Restriction map of poliovirus type 2 cDNA. Devel. Biol. Standard. 50, 301-309.

Agut H., Matsukura T., Bellocq C., **Dreano M.**, Nicolas JC., Girard M. 1981. Isolation and preliminary characterization of temperature sensitive mutants of poliovirus type 1. Ann. Virol. 132, 445-460

Submitted or In Preparation Publications

Sulpice T., Prunet-Marcassus B., Molveaux C.,' Cani P., Vitte P.A., Graber P., Dreano M., Burcelin R. An adiponectin-like molecule with antidiabetic properties. Antidiabetic properties of adiponectin. Submitted.

Published Patents and Patents Applications

Bhain B., Dreano M., Hantson J., Ogier V., Vitte P.A., Yen-Potin F. (8.2. 2008). Use of ACRP30 for the treatment and/or prevention of thrombosis and cancer. WO2007014798.

Dreano M.; Vitte P.A.; Cameron N.; Cotter M. (9.03. 2006) Use of IL-6 in vascular complications. WO2006025057

Dreano M.; Vitte P.A.(25.11.2005). IL-6 for therapy or preventing of chemotherapy-induced neuropathy. WO2005105135

Schiaffonati L.; Tiberio GAM.; **Dreano M.,** Garotta G. (7.7.2005). Use of IL-6 in the preparation of pharmaceutical composition for treating and preventing liver injury. WO2005060990.

Dreano M., Vitte PA. (7.7.2004) Use of gp130 activators in diabetic neuropathy. WO03033015.

Yonah N.; Susissa D.; Belzer I.; Antonetti A.; Smolarsky M.; **Dreano M.** (20.10.2003) Monoclonal antibodies to the human LDL receptor, their production and use. US2003186343.

Bromley P.; **Dreano M.**; Fischbach M.; Fouillet X.; Padieu P.; Voellmy R. (25.03.1997). Method for the inducible production of proteins in genetically modified eukaryotic host-cells multiplied in vivo. US5614381.

Dreano M., Bromley P., Voellmy R. (19.10.1989) Method for in vivo production and testing of proteins by recombinant gene expression in selected host-cells. WO089089822.

Bromley P.A., **Dreano M.**, Voellmy R. (13.12.1990) An improved heat-shock control method and system for the production of competent eukaryotic gene products. Patent Application EP 86 905251.

Bromley PA., **Dreano M.**, Voellmy R. (28.04.1989) A method for the expression of recombinant genes under the stimulation from an inducively expressed activator protein. WO8900603.